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ORTHOSTATIC MYOCLONUS ASSOCIATED WITH CASPR2 ANTIBODIES

Orthostatic myoclonus (OM) is a clinical phenomenon in which myoclonus of the lower limbs appears or becomes worse upon standing.¹ OM usually affects patients older than 65 years and may be a frequent cause of unsteadiness upon standing in the elderly.² Although the underlying etiology remains unclear, OM has predominantly been described in association with neurodegenerative diseases.¹ We describe a patient with OM in association with antibodies against contactin-associated protein-2 (Caspr2) whose symptoms markedly improved with immunotherapy.

Case report. A 68-year-old man presented to our department with a slowly progressive 2-year history of severe unsteadiness and involuntary jerks of his legs upon standing, along with coexisting burning pain of his feet and mild cognitive deficits. Symptoms first developed 1 month after a severe thoracic herpes zoster infection. On examination, there was slightly asymmetric (left more than right), non-stimulus sensitive, action myoclonus in the outstretched upper and lower limbs. Leg myoclonus was exacerbated upon standing and improved if the patient leaned forward on a chair. Gait was mildly unsteady with intermittent myoclonic jerks (video on the *Neurology*[®] Web site at Neurology.org). Distal allodynia and decreased sensation to pain and temperature were present in the legs.

Upon standing, surface EMG of the legs showed short (<50 ms), irregular, high-frequency (10- to 13-Hz) myoclonic bursts without intermittent silent periods (figure 1A). Homologous muscles in the right and left legs did not display significant coherence of bursts (figure 1B). Needle EMG of the vastus lateralis, tibialis anterior, biceps brachii, and abductor digiti minimi muscles were normal and without evidence of neuromyotonic discharges. Routine nerve conduction studies and sensory and motor evoked potentials of the arms and legs were unremarkable. MRI of the brain and spinal cord were normal; there was no evidence of thoracic myelopathy. EEG demonstrated generalized slowing (figure e-1). Autonomic testing showed marked orthostatic hypotension and reduced heartbeat variability due to sympathetic

failure. Cognitive testing revealed executive dysfunction, slight impairment of verbal memory, and impaired attention. The CSF revealed mild lymphocytic pleocytosis (10/ μ L), elevated total protein (516 mg/dL), and no intrathecal synthesis of immunoglobulins. Testing for antineuronal antibodies using rat brain immunohistochemistry and cell-based assays revealed Caspr2 immunoglobulin G antibodies (titer CSF: 1:360; serum: 1:6,400). Radioimmunoassay for voltage-gated potassium channel complex antibodies (VGKC) was positive in CSF (52 pmol/L) and serum (466 pmol/L). No other autoantibodies were detected. Whole-body CT and fluorodeoxyglucose PET did not show evidence of thymoma or other tumors.

Treatment with methylprednisolone (1 g, IV) was started but discontinued the following day due to the development of severe psychosis. The patient then started IV immunoglobulins (IVIg, 2 g/kg body weight), resulting in a few days in near complete resolution of the myoclonus and substantial improvement of his stance (video). The neuropathic pain improved; however, add-on therapy with carbamazepine was necessary. After 6 weeks, the OM recurred and again responded to IVIg. The patient has been maintained on IVIg every 8–12 weeks and remained stable over 12 months of follow-up.

Discussion. We report a patient with prominent unsteadiness upon standing and involuntary jerks of the lower limbs, whose clinical presentation and EMG findings fulfill the proposed criteria for OM.¹ The detection of Caspr2 antibodies and the near complete improvement after IVIg strongly support an autoimmune etiology of the OM in this patient.

Antibodies against Caspr2 were initially reported in patients with encephalitis or peripheral nerve hyperexcitability, or both (Morvan syndrome).^{3,4} However, the clinical spectrum of Caspr2-associated autoimmunity is still being characterized and chronic pain has been shown to be a frequent accompaniment.⁵ Our patient had a combination of OM with chronic neuropathic pain and mild cognitive deficits.

An autoimmune etiology has previously been proposed in a few patients with unsteadiness upon standing. Hegde et al.⁶ reported a patient with slow orthostatic tremor and superimposed myoclonus in association to an antibody against an unknown

Supplemental data
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Figure 1 Surface EMG recordings show noncoherent short, irregular, high-frequency myoclonus of the legs while standing

(A) Surface EMG recordings of both quadriceps and anterior tibial muscles and corresponding knee acceleration. Note the short duration (<50 ms), irregular frequency (10–13 Hz), nonsynchronized bursts of myoclonus in all examined muscles. (B) The lack of coherence of EMG bursts over the entire frequency range is demonstrated by Fourier analysis of the right and left quadriceps muscle. Mean coherence index (solid red) and 95% confidence interval (gray dashed lines) are not significantly above 0.4. Coherence index of 1 denotes perfect synchrony, while 0 denotes perfect asynchrony.

antigen who had an excellent response to IVIg. In a case series of patients with “isolated generalized polymyoclonus,” 14 of 19 patients had stance impairment and one had myoclonic knee buckling as in our patient.⁷ Five of these patients had cancer or anti-neuronal antibodies: 2 collapsin response mediator protein 5 (CRMP5) antibodies, 1 VGKC antibodies, 1 ganglionic acetylcholine receptor antibodies and breast cancer, and 1 breast cancer without antibodies,

although testing for recently described neuronal cell surface antibodies, such as Caspr2, was not available.⁷

Our case suggests that (1) treatable, immune-mediated forms of OM can be identified by assessment of neuronal antibodies, and (2) OM should be added to the spectrum of symptoms associated with Caspr2 antibodies.

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RADIOTHERAPY-INDUCED HEMICHOREA

A 76-year-old woman presented with 8 years of progressive right hand tremor. Initial examination demonstrated mild head tremor, voice tremor, right arm mild rest tremor, and moderate postural and kinetic tremor exacerbated by writing, and left hand mild postural tremor with no rest or kinetic components. Fahn-Tolosa-Marin (FTM) score was 35. Multiple medication trials, including β -blocker, primidone, and topiramate, were ineffective or associated with adverse effects. Deep brain stimulation (DBS) was offered, but the patient felt it was too invasive. She elected to undergo stereotactic radiosurgery (SRS), receiving 14,500 cGy to the left ventral intermediate (VIM) thalamic nucleus via linear accelerator-based SRS.

Within days of the procedure, the right hand tremor improved by 90%. However, 2.5 months later, a constant, nonstereotyped involuntary movement of the

right arm emerged, gradually progressive over 2 weeks. The patient denied weakness, sensory changes, or other significant neurologic deficits. Examination 3 months post-SRS was notable for mild choreiform movements of the right arm, involving the entire extremity from the hand to the shoulder. She continued to have a slight kinetic hand tremor bilaterally, but the right hand postural tremor was minimal, and the rest tremor had resolved. FTM score had improved to 21.

Brain MRI with and without contrast 3 months post-SRS showed an $8 \times 8 \times 8$ mm ring-enhancing lesion in the left thalamus with surrounding edema (figure); there were no other changes compared to the preoperative study. The patient was prescribed a 21-day dexamethasone taper. Within 5 days of steroid treatment, the chorea had subjectively improved by 70%.

Discussion. Current treatment options for medically refractory tremor include DBS, radiofrequency